REMARKS

Claims 53-60, 63-74, and 81-99 are pending in this application. Claims 53 and 95 have been amended to recite a lysate capable of inducing a humoral immune response against the TF antigen. Support for this amendment can be found in the specification, for example on page 22, paragraphs 2 and 3 (paragraphs [0078] and [0079] of U.S. Publication No. US 2006/0127419) and on page 42, Table 2, and page 44, first paragraph (paragraphs [0133] and [0135] of US 2006/0127419, respectively). Claim 98 has been amended to correct a typographical error noted by the Examiner. No new matter has been added by these amendments, and their entry is requested.

Finality of Office Action

In response to rejections under 35 U.S.C. § 102 and § 103 issued in the previous non-final Office Action, Applicants amended independent claims 53 and 95 by including the accession numbers of the NM-F9 and NM-D4 cell lines, which the Examiner indicated would obviate the rejections. However, the Examiner has now issued a Final rejection reiterating the rejections and introducing the new position that the amended claims are either anticipated or obvious because the claimed lysate is not strictly limited to lysate that has been "obtained by" the NM-F9 and NM-D4 tumor cell lines identified by their respective accession numbers. Regardless of the Examiner's prior indication that each of the rejections "would be obviated by amending independent claims 53 and 95 to recite that the NM-F9 cells of the claimed methods have the accession number DSM ACC2606 and the NM-D4 tumor cells of the claimed methods have the accession

number DSM ACC2605" (02/06/08 Office Action at pages 4, 9, and 10), the Examiner now asserts that a lysate "obtainable by" methods using NM-F9 or NM-D4 tumor cell lines with said accession numbers is still not free of the cited art.

Applicants understand that prosecution of an application is to be confined to as few actions as is consistent with a thorough consideration of its merits. However, Applicants also understand that before final rejection is in order, a clear issue should be developed between the Examiner and Applicant. "To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection." MPEP § 706.07. Applicants submit that their previous amendment was presented with a clear and distinct view to avoiding each of the Examiner's grounds of rejection, *as specifically guided* by the Examiner. Applicants also submit that the new position taken by the Examiner indicates that the Examiner did not fully apply the references in the first action. "The applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application." MPEP § 706.07. Applicants submit that they diligently sought to define their invention in the prior amendment, and in light of the outstanding Final rejection, respectfully submit that they have not received the cooperation of the Examiner with respect to identifying a clear issue justifying a final

action. Thus, Applicants hereby request reconsideration of the finality of the current Office Action.

Novelty

Claims 53, 55, 57, 63, 65, 67, 69, 71, 73, 81-85, 87, 89, 91, 92, 95, 96, and 99 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mivechi as evidenced by Lozzio and Lozzio. The Examiner asserts that cell lysates taught by Mivechi anticipate the cell lysate of the current claims.

Without conceding the Examiner's position, the Applicants have amended claims 53 and 95 to more clearly set forth the intended subject matter. The amended claims recite lysates that are capable of inducing a humoral immune response to the TF antigen. Applicants submit that the amended claims are novel over the prior art.

As stated in the MPEP, for a prior art reference to anticipate a claim under 35 U.S.C. § 102, the reference must teach every element of the claim. MPEP § 2131. The amended claims are drawn to products obtainable by inducing necrosis of TF-expressing NM-F9 or NM-D4 tumor cells and then obtaining a lysate therefrom. The Examiner alleges that Mivechi teaches vaccine compositions comprising lysates of heat-treated K562 cells, which are parental cells of the claimed NM-F9 and NM-D4 cells and, according to the Examiner, are comprised of "nearly identical matter." However, Mivechi teaches neither vaccine compositions nor lysates capable of inducing a humoral immune response to the TF antigen.

Mivechi is a comparative study of the heat sensitivities of three human myelogenous leukemia cell lines, performed to explore the potential therapeutic benefit

of hyperthermia in the treatment of leukemia. In Mivechi, each of the leukemia cell lines is subjected to various heat doses and assayed for cell survival by colony formation on soft agar plates. Neither the hyperthermia treatment nor the testing of cell survival involves the generation of cell lysates. Although Mivechi discloses lysates of the heat-treated cell lines, these lysates are sodium dodecyl sulfate-denatured gel samples generated for SDS-PAGE analysis of heat shock protein synthesis in the heat-treated cells. A person of skill in the art would not equate cell pellets resuspended in SDS-PAGE sample buffer with lysates suitable for vaccination and/or for loading into dendritic cells as described in the current claims. Although the Examiner asserts that Mivechi teaches vaccine compositions comprising lysates from the K562 cells, this assertion is simply false. Mivechi contains entirely no discussion of or reference to vaccine compositions or cancer immunotherapy. The study is exclusively focused on the potential for using heat treatment of leukemia cells as a cancer therapy. As the author states, "What is clear from these studies...is that this increased heat sensitivity of some leukemic cells as compared to normal bone marrow progenitors may be used to purge residual leukemic cells from bone marrow specimens" (Discussion, page 1956).

However, irrespective of whether Mivechi's SDS-sample buffer lysates could be considered lysates in the sense of the current claims, Mivechi's K562 lysates do not possess the features of the NM-F9 or NM-D4 lysates of the amended claims. As the Examiner notes, K562 cells are parental cells of the claimed NM-F9 and NM-D4 cells. Applicants generated NM-F9 cells by chemically mutagenizing K562 cells and specifically selecting single cell clones that stably express the tumor-specific Thomsen-

Friedenreich (TF) antigen, which normal K562 cells do not express. In Applicants' copending application USSN 10/568,098 (Publication No. US 2006/0292129), it is clearly demonstrated that NM-F9 cells express the TF antigen, while K562 cells do not (Figure 1, upper left and right panels, and Example 3, paragraphs [0111]-[0132], particularly paragraph [0127]). NM-D4 cells were generated by further mutagenizing NM-F9 cells and selecting single cell clones that stably express the tumor-specific TA-MUC1 antigen. Though K562 cells are parental cells of both the NM-F9 and NM-D4 cells and are thus likely to be comprised of a significant proportion of similar matter, the fact that NM-F9 and NM-D4 cells express the tumor-specific TF antigen while K562 cells do not creates a fundamental difference in the immunogenicity of the NM-F9 and NM-D4 lysates as compared to K562 cell lysates. This difference in immunogenicity facilitates the induction of a cancer cell-specific immune response that cannot be generated by any K562 lysates described in the prior art.

The Examiner cites Lozzio and Lozzio to show that the K562 cells in Mivechi are "genetically engineered, mutated, or infected by oncogenic viruses," which Applicants have described as preferred characteristics of the tumor cells used in the claimed process. Lozzio and Lozzio indicates that the abnormal Philadelphia chromosome known to be associated with chronic myelogenous leukemia is present in K562 leukemia cells. Applicants concede the fact that K562 cells have a genetic abnormality but note that this abnormality has no significance in relation to differences between K562 cells described by Mivechi and the NM-F9 and NM-D4 cells of the amended claims.

In light of the documented difference between K562 and the NM-F9/D4 cells of the amended claims, Applicants submit that Mivechi does not anticipate the claims, and specifically request withdrawal of this rejection.

Nonobviousness

I. Claims 53-60, 67-74, 81-83, 86, and 91-99 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Subjeck et al. in view of Yoshima et al. The Examiner has maintained the assertion that Subjeck teaches a lysate of mutated tumor cells obtainable by inducing necrosis by heat treatment and lysing said necrotic tumor cells, and that Yoshima teaches NM-F9 or NM-D4 cells that one of skill in the art would have been motivated to use as the mutated tumor cells of Subjeck.

Applicants submit that the amended claims are not obvious over Subjeck in view of Yoshima. Subjeck teaches immunogenic polypeptides that can be isolated from mutated tumor cells. The Examiner recognizes that Subjeck does not teach lysates using NM-F9 or NM-D4 tumor cells, but asserts that this deficiency is remedied by Yoshima's teaching of K562 human leukemia cells that are genetically engineered, mutated, or infected by oncogenic viruses. The amended claims state that the lysates are capable of inducing a humoral immune response against the TF antigen. As discussed above and demonstrated in Applicants' copending application USSN 10/568,098, Applicants' NM-F9 and NM-D4 cells are distinct from K562 cells, because they are mutagenized variants of K562 cells that stably express the tumor-specific TF antigen, which normal K562 cells do not. Yoshima's K562 cells are transfected with a

gene for a chimeric transcription factor for the *hsp70* gene. The Examiner states that these transfected cells *are* NM-F9 and NM-D4 cells based on the definition of these cells as "derived from the human myelogenous leukemia cell line K562" in the specification (page 22; paragraph [0079] is US 2006/0127419). However, the specification also indicates, as described above, that the NM-F9 and NM-D4 cells are TF-positive, which K562 cells are not. No evidence is present in Yoshima that the introduction of an *hsp70* transcription factor into K562 cells induces the cells to express the TF antigen, nor would one of skill have any reason to predict that it would. Therefore, Yoshima's K562 cells cannot elicit a response against the TF antigen, and cannot remedy the defects of Subjeck in rendering the amended claims obvious. Accordingly, Applicants request withdrawal of this rejection.

II. Claims 53-60, 63-74, and 81-99 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Mivechi as applied to claims 53, 55, 57, 63, 65, 67, 69, 71, 73, 81-85, 87, 89, 91, 92, 95, 96, and 99 and further in view of Subjeck. The Examiner asserts that one of ordinary skill in the art would have been motivated to use the NM-F9 and NM-D4 cells taught by Mivechi as the mutated tumor cells in producing the vaccine taught by Subjeck. As described above, Mivechi teaches K562 cells that do not express the TF antigen, and it therefore cannot render obvious the claimed lysates capable of eliciting a humoral immune response against the TF antigen. Subjeck teaches immunogenic polypeptides that can be isolated from mutated tumor cells and optionally introduced into dendritic cells to elicit an immune response. Subjeck does not teach

NM-F9, NM-D4 cells, nor any other cells expressing the TF antigen, and therefore cannot remedy the deficiencies of Mivechi. Because neither Mivechi nor Subjeck contains a teaching, suggestion, or motivation to generate lysates capable of eliciting a humoral immune response against the TF antigen, Applicants submit that the amended claims are not obvious over the cited art and request withdrawal of this rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and timely allowance of the claims. Applicants invite the Examiner to call the undersigned Applicants' representative with any questions or comments.

Please grant any additional extensions of time required to enter this response and charge any additional fees to deposit account 06-0916.

Respectfully submitted,

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